II. Remarks/ Arguments

Reconsideration of the application in view of the above amendments and the following remarks is requested.

Claims 1, 4, 7-8, 12-16, 57-60, and 69 are pending in the applications. Claims 1, 4, 8, and 69 are independent.

Claims 1, 4, 7-8, 12-16, 57-60, and 69 were rejected under 35 U.S.C. § 112, first paragraph, written description requirement, for the reasons discussed on pages 3-4 of the Office Action. Applicants respectfully traverse this rejection on the ground that the person of ordinary skill in the art would readily apprehend that Applicants were in possession of the claimed invention as of the application filing date. Nevertheless, solely to advance this application to issue, Applicants have amended the claims to remove any reference to the term "prodrug."

Claims 1, 4, 7-8, 12-16, 57-60, and 69 were rejected under 35 U.S.C. § 112, first paragraph, enablement requirement, for the reasons discussed on pages 4-6 of the Office Action. Applicants respectfully traverse this rejection on the ground that the person of ordinary skill in the art would be readily enabled to make and use the invention given the specification and Drawings, without undue experimentation. The Examiner states that the Applicants have not provided the necessary direction such that one of skill in the art would be able to use CR4, or any of the other non-elected compounds, in order to treat an animal for cancer.

The Examiner specifically states that claims 57-60 claim treatment of animals which are "at risk for developing vascularised solid tumor", but that the Applicants have not defined how one of skill in the art would know who is at risk. Further, the Examiner states that it is not shown how to prevent the disease by treating those who are merely at risk, before they develop it.

Applicants respectfully submit that a person skilled in the art would know who is "at risk for developing vascularised solid tumor". Further, Applicants submit that information is available that provides a person with such information, for example the National Cancer Institute publishes information pertaining to risk factors for different types of cancer. It is well known that risk factors for breast cancer include mutations in the BRCA1 or BRCA2 genes (Bishop DT, Eur. J. Cancer. 1994, 30A(12):1738-39), family history of disease, prior clinical incidence and age (http://www.cancer.gov/cancertopics/pdq/genetics/breast-and-

ovarian/HealthProfessional/page2 attached hereto). Similar guidelines are also provided for prostate cancer and melanoma, see (http://www.cancer.gov/cancertopics/pdq/genetics/prostate/Health Professional/page6, and http://www.cancer.gov/cancertopics/pdq/screening/skin/HealthProfessional/page3 both attached hereto). Applicants respectfully submit that a person skilled in the art, having access to this information, would be able to assess who is "at risk for developing vascularised solid tumor".

The Examiner further states that "Applicants have only shown cell culture data, and has not shown treating affected patients or shown an art recognized correlation between the data shown and the scope of the claimed invention". The Examiner states that there is "merely an unsubstantiated assertion with no evidence to support the contention that the *in vitro* studies of the specification are indicative of *in vivo* activity."

Applicants respectfully disagree with the Examiner. As indicated by the Examiner, Applicants have provided in vitro data showing the inhibition of VEGF, by the compounds of interest, in 3 breast cancer cell lines (HTB-133, HTB-131 and MDA-231), prostate cancer cell line (HTB-181), melanoma cell line (HTB-72) and human umbilical vascular endothelial cell line (CR2-1730).

Applicants respectfully submit that these cell lines are known cell lines that are used in the art, including for the identification of anticancer drugs. With respect to the elected disease breast cancer, Applicants respectfully submit that the MDA-231 cells are commonly used to screen for anticancer drugs that will be effective against breast cancer. For example, the US National Cancer Institute operates a service for the cancer research community in which they utilize 60 tumor cell lines (NCI60) representing various types of cancer to screen for anticancer drugs http://dtp.nci.nih.gov/screening.html (attached). The MDA-231 cell line is one of the NCI60 cell lines used as representative of breast cancer http://dtp.nci.nih.gov/docs/misc/common_files/cell_list.html (attached). Therefore, the NCI is using MDA-231 cells for *in vitro* drug screens to identify anticancer drugs.

The specification also includes the HTB-133 breast cancer cell line and a VEGF-receptor negative variant of that cell line, HTB-131. Applicants respectfully submit that the demonstration of CR4 activity in multiple breast cancer cell lines, as opposed to only one, further enforces the predictive value of the *in vitro* tests for *in vivo* anticancer activity.

Applicants respectfully submit that the information provided demonstrates that these cell lines are known and are used in the art and that a person skilled in the art would recognise that the *in vitro* data and results provided are indicative of the claimed *in vivo* subject matter. Therefore, Applicants submit that sufficient teaching has been provided to allow one to have a reasonable expectation of success in transferring the *in vitro* method to treat affected patients. Any requirement to supply specific *in vivo* data places an unnecessary burden on the Applicants and any amendment in the claims to include reference to "*in vitro*" methods would unfairly restricts the scope of Applicants' claims.

Claim Rejections- 35 U.S.C.§103(a)

The Examiner has rejected claims 1, 4, 7-8, 12-16, 57-60 and 69 under 35 U.S.C. 103(a) as being unpatentable over Roifman et al. (WO 01/79158 A2) in view of Bessette et al. (US 2003/0017215 A1) in further view of Butler et al. (US 5,486,457). The Examiner states that it would have been obvious to one of ordinary skill in the art at the time of the invention that the method of Roifman et al. would be useful for breast cancer in addition to the cancers named as the compounds are shown to inhibit cell proliferation and cell proliferation is also linked to breast cancer.

Applicants respectfully disagree that the subject matter of the pending claims is obvious in light of the cited references.

The pending claims are directed to a method of inhibiting secretion of vascular endothelial growth factor in an animal, a method of inhibiting an effect of vascular endothelial growth factor in an animal in need of such inhibition and a method of treating a disorder caused or contributed to by vascular endothelial growth factor in an animal. The pending claims are all related to the inhibition of vascular endothelial growth factor (VEGF). As stated in the Summary of the Invention section, the present application is directed to the "unexpected discovery" that certain compounds are capable of inhibiting the activity of VEGF. In addition, *in vitro* data is provided to show that the exemplified compounds inhibit VEGF secretion, see Examples 15-18.

Applicants respectfully submit that there is no teaching or suggestion, in any of the cited references, of the specific use of these compounds for the inhibition of VEGF. Therefore, although as stated the by the Examiner, Roifman teaches, for example, the structure of CR4,

there is no discussion of the use of CR4 for the inhibition of VEGF. In addition, there is no specific discussion of VEGF in either Bessette et al. or Butler et al.. Applicants therefore, respectfully submit that a person skilled in the art, given the teachings in the cited art, would not be led to the subject matter of the pending claims. Withdrawal of this objection is respectfully requested.

In view of the above remarks, and amendments submitted herewith, Applicants respectfully submit that independent amended claims 1, 4, and 8 are novel and inventive over the cited art. Further, as the remaining dependent claims are dependent on these independent claims, Applicants similarly respectfully submit that these claims are novel and inventive over the cited art. Applicants respectfully request reconsideration and allowance of the application.

If the Examiner has further concerns, he is encouraged to contact Applicants' undersigned agent if the Examiner considers that a telephone conference would be of assistance in this matter.

Dated: January 15, 2009

Respectfully submitted,

/Richard P. Bauer/

Agent for Applicants
Richard P. Bauer
Registration Number 31,588

PATENT ADMINISTRATOR
Katten Muchin Rosenman LLP
2900 K Street NW / Suite 200
Washington, DC 20007-5118
Facsimile: (202) 298-7570

Genetics of Breast and Ovarian Cancer (PDQÂ®)

Health Professional Version

Last Modifie

Introduction

General Information

Â [*Note: Many of the medical and scientific terms used in this summary are found in the NC Genetics Terms. When a linked term is clicked, the definition will appear in a separate wind*

Among women, breast cancer is the most commonly diagnosed cancer after nonmelanoma and is the second leading cause of cancer deaths after lung cancer. In 2008, an estimated cases will be diagnosed, and 40,480 deaths from breast cancer will occur.[1] The incidence cancer, particularly for estrogen receptor-positive cancers occurring after age 50 years, has faster rate since 2003; this may be temporally related to a decrease in hormone replacemei following early reports from the Womenâ€™s Health Initiative.[2] Ovarian cancer is the eigh common cancer, with an estimated 21,650 new cases in 2008, but is the fifth most deadly, estimated 15,520 deaths in 2008.[1] (Refer to the PDQ summary on Breast Cancer Treatm Epithelial Cancer Treatment for more information on breast cancer and ovarian cancer rate and management.)

A possible genetic contribution to both breast and ovarian cancer risk is indicated by the inc incidence of these cancers among women with a family history (see the Family History as a Breast Cancer and the Family History as a Risk Factor for Ovarian Cancer sections below), observation of rare families in which multiple family members are affected with breast and/c cancer, in a pattern compatible with autosomal dominant inheritance of cancer susceptibilit studies of families (linkage analysis) have subsequently proven the existence of autosomal predispositions to breast and ovarian cancer and have led to the identification of several hig genes as the cause of inherited cancer risk in many cancer-prone families. (Refer to the PD Cancer Genetics Overview for more information on linkage analysis.) Mutations in these ge

NCI Highlights

Report to Nation Finds Declines in Cancer Incidence, Death Rates

High Dose Chemotherapy Prolongs Survival for Leukemia

Prostate Cancer Study Shows No Benefit for Selenium, Vitamin E

The Nation's Investment in Cancer Research FY 2009

Past Highlights

the general population and are estimated to account for no more than 5% to 10% of breast cancer cases overall. It is likely that other genetic factors contribute to the etiology of some cancers.

Family History as a Risk Factor for Breast Cancer

In cross-sectional studies of adult populations, 5% to 10% of women have a mother or siste cancer, and about twice as many have either a first-degree relative or a second-degree rela cancer.[3-6] The risk conferred by a family history of breast cancer has been assessed in b and cohort studies, using volunteer and population-based samples, with generally consistei pooled analysis of 38 studies, the relative risk (RR) of breast cancer conferred by a first-deg breast cancer was 2.1 (95% confidence interval [CI], 2.0-2.2).[7] Risk increases with the nu relatives and age at diagnosis.[4,5,7] Refer to the Penetrance of Mutations section for a dis familial risk for women from families with *BRCA1/2* mutations who themselves test negative mutation.

Family History as a Risk Factor for Ovarian Cancer

Although reproductive, demographic, and lifestyle factors affect risk of ovarian cancer, the s ovarian cancer risk factor is a family history of the disease. A large meta-analysis of 15 pub estimated an odds ratio (OR) of 3.1 for the risk of ovarian cancer associated with at least or relative with ovarian cancer.[8]

Autosomal Dominant Inheritance of Breast/Ovarian Cancer Predispositio

Autosomal dominant inheritance of breast/ovarian cancer is characterized by transmission predisposition from generation to generation, through either the motherâ€™s or the fatherâ family, with the following characteristics:

- Inheritance risk of 50%. When a parent carries an autosomal dominant genetic predisp child has a 50:50 chance of inheriting the predisposition. Although the risk of inheriting predisposition is 50%, not everyone with the predisposition will develop cancer becaus penetrance and/or gender-restricted or gender-related expression.
- Both males and females can inherit and transmit an autosomal dominant cancer predis who inherits a cancer predisposition and shows no evidence of it can still pass the alte his sons and daughters.

Breast and ovarian cancer are components of several autosomal dominant cancer syndrom syndromes most strongly associated with both cancers are *BRCA1* or *BRCA2* mutation syn cancer is also a common feature of Li-Fraumeni syndrome due to *TP53* mutations; of Cowc due to *PTEN* mutations; and with mutations in *CHEK2* .[9] Other genetic syndromes that m breast cancer as an associated feature include heterozygous carriers of the ataxia telangie and Peutz-Jeghers syndrome. Ovarian cancer has also been associated with Lynch syndro nevus (Gorlin) syndrome (OMIM), and multiple endocrine neoplasia type 1 (MEN1) (OMIM) each of these genes produce different clinical phenotypes of characteristic malignancies an instances, associated nonmalignant abnormalities.

The family characteristics that suggest hereditary breast and ovarian cancer predisposition following:

- Cancers typically occur at an earlier age than in sporadic cases (defined as cases not genetic risk).
- Two or more primary cancers in a single individual. These could be multiple primary ca same type (e.g., bilateral breast cancer) or primary cancer of different types (e.g., brea cancer in the same individual).
- Cases of male breast cancer.
- Possible increased risk of other selected cancers and benign features for males and fe the Major Genes section of this summary for more information.)

There are no pathognomonic features distinguishing breast and ovarian cancers occurring i *BRCA2* mutation carriers with those occurring in noncarriers. Breast cancers occurring in *B* carriers are more likely to be estrogen receptor (ER)-negative, progesterone receptor (PR)- HER2/neu receptor-negative and have a basal phenotype. *BRCA1*-associated ovarian canc to be of mucinous or borderline histopathology. [Refer to the Pathology/Prognosis of Breast Pathology/Prognosis of Ovarian Cancer sections for more information.]

Difficulties in Identifying a Family History of Breast and Ovarian Cancer I

When using family history to assess risk, the accuracy and completeness of family history c taken into account. A reported family history may be erroneous, or a person may be unawa affected with cancer. In addition, small family sizes and premature deaths may limit the info obtained from a family history. Breast or ovarian cancer on the paternal side of the family u: more distant relatives than on the maternal side and thus may be more difficult to obtain. W self-reported information with independently verified cases, the sensitivity of a history of bre relatively high, at 83% to 97%, but lower for ovarian cancer, at 60%.[10,11]

Other Risk Factors for Breast Cancer

Other risk factors for breast cancer include age, reproductive and menstrual history, hormo radiation exposure, mammographic breast density, alcohol intake, physical activity, anthrop variables, and a history of benign breast disease. (Refer to the PDQ summary on Preventio Cancer for more information.) These factors are considered in more detail in numerous revi including among *BRCA1/BRCA2* mutation carriers.[14] Brief summaries are given below, hi where possible, the effect of these risk factors in women who are genetically susceptible to (More information about their effects in *BRCA1/BRCA2* mutation carriers can be found in th Interventions later in this document.)

Age

Cumulative risk of breast cancer increases with age, with most breast cancers occurring aft [15] In women with a genetic susceptibility, breast cancer, and to a lesser degree, ovarian c occur at an earlier age than in sporadic cases.

Reproductive and menstrual history

Breast cancer risk increases with early menarche and late menopause, and is reduced by e term pregnancy. Although results have been complex and may be gene dependent, severa suggested that the influence of these factors on risk in *BRCA1/BRCA2* mutation carriers ap similar to noncarriers.[14,16]

Oral contraceptives

Oral contraceptives may produce a slight increase in breast cancer risk among long-term u: appears to be a short-term effect. In a meta-analysis of data from 54 studies, the risk of bre associated with oral contraceptive use did not vary according to a family history of breast ca

Oral contraceptives are sometimes recommended for ovarian cancer prevention in *BRCA1* mutation carriers, but studies of their effect on breast cancer risk have been inconsistent.[1

Hormone Replacement Therapy

Data exist from both observational and randomized clinical trials regarding the association b postmenopausal hormone replacement therapy (HRT) and breast cancer. A meta-analysis observational studies indicated a RR of breast cancer of 1.35 (95% CI, 1.21â€"1.49) for wo used HRT for 5 or more years after menopause.[21] The Women's Health Initiative (WHI), a controlled trial of about 160,000 postmenopausal women, investigated the risks and benefit estrogen-plus-progestin arm of the study, which randomized more than 16,000 women to re HRT or placebo, was halted early because health risks exceeded benefits.[22,23] Adverse prompting closure included significant increase in both total (245 vs. 185 cases) and invasiv cases) breast cancers (RR = 1.24; 95% CI, 1.02â€"1.5, *P* <.001) and increased risks of cor disease, stroke, and pulmonary embolism. Similar findings were seen in the estrogen-proge

prospective observational Million Womenâ€™s Study in the United Kingdom.[24] The risk c was not elevated, however, in women randomly assigned to estrogen-only versus placebo i (RR = 0.77; 95% CI, 0.59â€“1.01). Eligibility for the estrogen-only arm of this study requirec and 40% of these patients also had undergone oophorectomy, which potentially could have breast cancer risk.[25]

The association between HRT and breast cancer risk among women with a family history o has not been consistent; some studies suggest risk is particularly elevated among women v history, while others have not found evidence for an interaction between these factors.[26-3 increased risk of breast cancer associated with HRT use in the large meta-analysis did not significantly between subjects with and without a family history. The WHI study has not repo stratified on breast cancer family history, and subjects have not been systematically tested mutations.[23] Short-term use of hormones for treatment of menopausal symptoms appear or no breast cancer risk.[21,31] The effect of HRT on breast cancer risk among carriers of *E BRCA2* mutations has been studied only in the context of bilateral risk-reducing oophorectc short-term replacement does not appear to reduce the protective effect of oophorectomy or risk.[32]

Radiation exposure

Observations in survivors of the atomic bombings of Hiroshima and Nagasaki and in womer received therapeutic radiation treatments to the chest and upper body document increased risk as a result of radiation exposure. The significance of this risk factor in women with a ge susceptibility to breast cancer is unclear.

Preliminary data suggest that increased sensitivity to radiation could be a cause of cancer s carriers of *BRCA1* and *BRCA2* mutations,[33-36] and in association with germline *ATM* anc mutations.[37,38] Since *BRCA1/2* mutation carriers are heterozygotes, however, radiation s occur only after a somatic mutation has damaged the normal copy of the gene.

The possibility that genetic susceptibility to breast cancer occurs via a mechanism of radiati raises questions about radiation exposure. It is possible that diagnostic radiation exposure, mammography, poses more risk in genetically susceptible women than in women of averag Therapeutic radiation could also pose carcinogenic risk. A cohort study of *BRCA1* and *BRC* carriers treated with breast-conserving therapy, however, showed no evidence of increased sensitivity or sequelae in the breast, lung, or bone marrow of mutation carriers.[39] Convers sensitivity could make tumors in women with genetic susceptibility to breast cancer more re radiation treatment. Studies examining the impact of mammography and chest x-ray exposi and *BRCA2* mutation carriers have had conflicting results.[40,41] (Refer to text on Radiatio Interventions section of this summary for more information.)

Alcohol intake

The risk of breast cancer increases by approximately 10% for each 10g of daily alcohol inta (approximately 1 drink or less) in the general population.[42,43] One study of *BRCA1/BRCA* carriers found no increased risk associated with alcohol consumption.[44]

Physical Activity and Anthropometry

Weight gain and being overweight are commonly recognized risk factors for breast cancer. overweight women are most commonly observed to be at increased risk of postmenopausa and at reduced risk of premenopausal breast cancer. Sedentary lifestyle may also be a risk These factors have not been systematically evaluated in women with a positive family histo cancer or in carriers of cancer-predisposing mutations, but one study suggested a reduced associated with exercise among *BRCA1* and *BRCA2* mutation carriers.[46]

Benign breast disease and mammographic density

Benign breast disease (BBD) is a risk factor for breast cancer, independent of the effects of factors for breast cancer (age, age at menarche, age at first live birth, and family history of I [47] There may also be an association between benign breast disease and family history of [48]

An increased risk of breast cancer has also been demonstrated for women who have increa breast tissue as assessed by mammogram,[47,49,50] and breast density may have a gene its etiology.[51-53]

Other factors

Other risk factors, including those that are only weakly associated with breast cancer and th been inconsistently associated with the disease in epidemiologic studies (e.g., cigarette sm important in subgroups of women defined according to genotype. For example, some studie suggested that certain N-acetyl transferase alleles may influence female smokersâ€™ risk breast cancer.[54] One study [55] found a reduced risk of breast cancer among *BRCA1/2* m who smoked, but an expanded follow-up study failed to find an association.[56]

Other Risk Factors for Ovarian Cancer

Factors that increase risk for ovarian cancer include increasing age and nulliparity, while th decrease risk include surgical history and oral contraceptives.[57,58] (Refer to the PDQ sur Prevention of Ovarian Cancer for more information.) Relatively few studies have addressed these risk factors in women who are genetically susceptible to ovarian cancer. (Refer to the Modification section for more information.)

Age

Ovarian cancer incidence rises in a linear fashion from age 30 years to age 50 years and c increase, though at a slower rate, thereafter. Before age 30 years, the risk of developing ep cancer is remote; even in hereditary cancer families.[59]

Reproductive history

Nulliparity is consistently associated with an increased risk of ovarian cancer, including amc *BRCA1/BRCA2* mutation carriers.[60] Risk may also be increased among women who have drugs, especially those who remain nulligravid.[57,61] Evidence is growing that the use of n is associated with an increased risk of ovarian cancer, particularly in long-time users and us sequential estrogen-progesterone schedules.[62-65]

Surgical history

Bilateral tubal ligation and hysterectomy are associated with reduced ovarian cancer risk,[5 including in *BRCA1/BRCA2* mutation carriers.[68] Ovarian cancer risk is reduced more thar with documented *BRCA1* or *BRCA2* mutations who chose risk-reducing salpingo-oophorec this same population, prophylactic removal of the ovaries also resulted in a nearly 50% redu of subsequent breast cancer.[69,70] For further information on these studies refer to the Ris Salpingo-Oophorectomy section of this summary.

Oral contraceptives

Use of oral contraceptives for 4 or more years is associated with an approximately 50% red cancer risk in the general population.[57,58] A majority of, but not all, studies also support c contraceptives being protective among *BRCA1/ BRCA2* mutation carriers.[60,71-74]

Models for Prediction of Breast Cancer Risk

Models to predict an individualâ€™s lifetime risk for developing breast cancer are available models exist to predict an individualâ€™s likelihood of having a *BRCA1* or *BRCA2* mutation information on these models refer to the Models for Prediction of the Likelihood of a BRCA1 Mutation section of this summary. Not all models can be appropriately applied for all patient is appropriate only when the patientâ€™s characteristics and family history are similar to th population on which the model was based. The table, Characteristics of the Gail and Claus summarizes the salient aspects of the risk assessment models and is designed to aid in ch that best applies to a particular individual.

Two models for predicting breast cancer risk, the Claus model [75,76] and the Gail model,[7 used in research studies and clinical counseling. Both have limitations, and the risk estimat the two models may differ for an individual patient. These models, however, represent the b currently available for individual risk assessment.

It is important to note that these models will significantly underestimate breast cancer risk fc families with hereditary breast cancer susceptibility syndromes. In those cases, Mendelian r apply. A 3-generation cancer family history is taken before applying any model. (Refer to th on Cancer Genetics Risk Assessment and Counseling for more information on Taking a Fa Generally, the Claus or Gail models should not be the sole model used for families with one characteristics:

- Three individuals with breast or ovarian cancer (especially when one or more breast ca diagnosed before age 50 years).
- A woman who has both breast and ovarian cancer.
- Ashkenazi Jewish ancestry with at least one case of breast or ovarian cancer (as these more likely to have a hereditary cancer susceptibility syndrome).

Table 1. Characteristics of the Gail and Claus Models[a]

Â	Gail ModelÂ	Claus M
Data derived from	Breast Cancer Detection Demonstration Project (BCDDP) Study	Cancer and Steroid Study
Study population	2,852 cases, aged â‰¥35 years	4,730 cases, aged 2
	In situ and invasive cancer	Invasive cancer
	3,146 controls	4,688 controls
	Caucasian	Caucasian
	Annual breast screening	Not routinely screer
Family history characteristics	First-degree relatives with breast cancer	First-degree or secc relatives with breas
		Age of onset in rela
Other characteristics	Current age	Current age
	Age at menarche	
	Age at first live birth	
	Number of breast biopsies	
	Atypical hyperplasia in breast biopsy	
	Race (included in the most current version of the Gail model)	
Strengths	Incorporates:	Incorporates:
	Risk factors other than family history	Paternal as well as
		Age at onset of brea
		Family history of ov
Limitations	Underestimates risk in hereditary families	May underestimate families
	Number of breast biopsies without atypical hyperplasia may cause inflated risk estimates	May not be applicat combinations of affe
		Does not include ris family history
	Does not incorporate:	
	Paternal family history of breast cancer or any family history of ovarian cancer	

	Age at onset of breast cancer in relatives	
	All known risk factors for breast cancer [80]	
Best application	For individuals with no family history of breast cancer or 1 first-degree relative with breast cancer, aged â‰¥50 years	For individuals with degree or second-d breast cancer
	For determining eligibility for chemoprevention studies	
[a]*Adapted from Domchek et al.,[78] Rubenstein et al.,[79] and Rhodes.[80]*		

The Gail model has been found to be reasonably accurate at predicting breast cancer risk i of white women who undergo annual screening mammography.[81-85] While the model is r predicting the number of breast cancer cases expected in a group of women from the same it is less reliable in predicting risk for individual patients. Risk can be overestimated in:

- Nonadherent women (i.e., does not adhere to screening recommendations).[81,82]
- Women in the highest risk strata.[84]

Risk could be underestimated in the lowest risk strata.[84] Earlier studies [81,82] suggestec overpredicted in younger women and underpredicted in older women. More recent studies | modified Gail model (which is currently used) found it performed well in all age groups. Furt needed to establish the validity of the Gail model in minority populations.[85]

A study of 491 women aged 18 to 74 years with a family history of breast cancer compared Gail model to the Claus model in predicting breast cancer risk.[86] The two models were pc correlated (r = .55). The Gail model estimates were higher than the Claus model estimates participants. Presentation and discussion of both the Gail and Claus models risk estimates the counseling setting.

The Gail model is the basis for the Breast Cancer Risk Assessment Tool, a computer progr available from the NCI by calling the Cancer Information Service at 1-800-4-CANCER (1-8C TTY at 1-800-332-8615). This version of the Gail Model estimates only the risk of invasive b

The Tyrer-Cuzick model incorporates both genetic and non-genetic factors.[87] A three gen is used to estimate the likelihood that an individual carries either a *BRCA1/BRCA2* mutatior hypothetical low penetrance gene. In addition, the model incorporates personal risk factors body mass index, height, and age at menarche, menopause and first live birth. Both genetic nongenetic factors are combined to develop a risk estimate. Although powerful, the model a time is less accessible to primary care providers than the Gail and Claus models. The BOAI examines family history to estimate breast cancer risk, and also incorporates both *BRCA1/2* *BRCA1/2* genetic risk factors.[88]

Other models incorporating breast density have been developed, but are not ready for clinic the future, models may be developed or refined to include such factors as breast density ar biomarkers.

References

1. American Cancer Society.: Cancer Facts and Figures 2008. Atlanta, Ga: American (2008. Also available online. Last accessed October 1, 2008.Â
2. Ravdin PM, Cronin KA, Howlader N, et al.: The decrease in breast-cancer incidence United States. N Engl J Med 356 (16): 1670-4, 2007.Â [PUBMED Abstract]
3. Yang Q, Khoury MJ, Rodriguez C, et al.: Family history score as a predictor of breas mortality: prospective data from the Cancer Prevention Study II, United States, 198: Epidemiol 147 (7): 652-9, 1998.Â [PUBMED Abstract]
4. Colditz GA, Willett WC, Hunter DJ, et al.: Family history, age, and risk of breast can data from the Nurses' Health Study. JAMA 270 (3): 338-43, 1993.Â [PUBMED Abstrac

5. Slattery ML, Kerber RA: A comprehensive evaluation of family history and breast ca Utah Population Database. JAMA 270 (13): 1563-8, 1993.Â [PUBMED Abstract]

6. Johnson N, Lancaster T, Fuller A, et al.: The prevalence of a family history of cance practice. Fam Pract 12 (3): 287-9, 1995.Â [PUBMED Abstract]

7. Pharoah PD, Day NE, Duffy S, et al.: Family history and the risk of breast cancer: a review and meta-analysis. Int J Cancer 71 (5): 800-9, 1997.Â [PUBMED Abstract]

8. Stratton JF, Pharoah P, Smith SK, et al.: A systematic review and meta-analysis of and risk of ovarian cancer. Br J Obstet Gynaecol 105 (5): 493-9, 1998.Â [PUBMED A

9. Lindor NM, McMaster ML, Lindor CJ, et al.: Concise handbook of familial cancer su syndromes - second edition. J Natl Cancer Inst Monogr (38): 1-93, 2008.Â [PUBMEI

10. Kerber RA, Slattery ML: Comparison of self-reported and database-linked family his data in a case-control study. Am J Epidemiol 146 (3): 244-8, 1997.Â [PUBMED Abstra

11. Parent ME, Ghadirian P, Lacroix A, et al.: The reliability of recollections of family his implications for the medical provider. J Cancer Educ 12 (2): 114-20, 1997 Summer. Abstract]

12. Key TJ, Verkasalo PK, Banks E: Epidemiology of breast cancer. Lancet Oncol 2 (3) 2001.Â [PUBMED Abstract]

13. Hankinson S, Hunter D: Breast cancer. In: Adami H, Hunter D, Trichopoulos D, eds. Cancer Epidemiology. New York, NY: Oxford University Press, 2002, pp 301-39.Â

14. Narod SA: Modifiers of risk of hereditary breast and ovarian cancer. Nat Rev Cance 2002.Â [PUBMED Abstract]

15. Feuer EJ, Wun LM, Boring CC, et al.: The lifetime risk of developing breast cancer. Inst 85 (11): 892-7, 1993.Â [PUBMED Abstract]

16. Antoniou AC, Shenton A, Maher ER, et al.: Parity and breast cancer risk among BR BRCA2 mutation carriers. Breast Cancer Res 8 (6): R72, 2006.Â [PUBMED Abstract]

17. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual da women with breast cancer and 100 239 women without breast cancer from 54 epide studies. Collaborative Group on Hormonal Factors in Breast Cancer. Lancet 347 (9(1996.Â [PUBMED Abstract]

18. Ursin G, Henderson BE, Haile RW, et al.: Does oral contraceptive use increase the cancer in women with BRCA1/BRCA2 mutations more than in other women? Cance 3678-81, 1997.Â [PUBMED Abstract]

19. Narod SA, DubÃ© MP, Klijn J, et al.: Oral contraceptives and the risk of breast canc and BRCA2 mutation carriers. J Natl Cancer Inst 94 (23): 1773-9, 2002.Â [PUBMED

20. Milne RL, Knight JA, John EM, et al.: Oral contraceptive use and risk of early-onset carriers and noncarriers of BRCA1 and BRCA2 mutations. Cancer Epidemiol Bioma (2): 350-6, 2005.Â [PUBMED Abstract]

21. Breast cancer and hormone replacement therapy: collaborative reanalysis of data fr epidemiological studies of 52,705 women with breast cancer and 108,411 women w cancer. Collaborative Group on Hormonal Factors in Breast Cancer. Lancet 350 (9(1997.Â [PUBMED Abstract]

22. Writing Group for the Women's Health Initiative Investigators.: Risks and benefits of progestin in healthy postmenopausal women: principal results From the Women's H randomized controlled trial. JAMA 288 (3): 321-33, 2002.Â [PUBMED Abstract]

23. Chlebowski RT, Hendrix SL, Langer RD, et al.: Influence of estrogen plus progestin cancer and mammography in healthy postmenopausal women: the Women's Healtr Randomized Trial. JAMA 289 (24): 3243-53, 2003.Â [PUBMED Abstract]

24. Beral V; Million Women Study Collaborators.: Breast cancer and hormone-replacem the Million Women Study. Lancet 362 (9382): 419-27, 2003.Â [PUBMED Abstract]

25. Anderson GL, Limacher M, Assaf AR, et al.: Effects of conjugated equine estrogen i postmenopausal women with hysterectomy: the Women's Health Initiative randomiz trial. JAMA 291 (14): 1701-12, 2004.Â [PUBMED Abstract]

26. Schuurman AG, van den Brandt PA, Goldbohm RA: Exogenous hormone use and tl postmenopausal breast cancer: results from The Netherlands Cohort Study. Cancer 6 (5): 416-24, 1995.Â [PUBMED Abstract]

27. Steinberg KK, Thacker SB, Smith SJ, et al.: A meta-analysis of the effect of estroge therapy on the risk of breast cancer. JAMA 265 (15): 1985-90, 1991.Â [PUBMED Abs

28. Sellers TA, Mink PJ, Cerhan JR, et al.: The role of hormone replacement therapy in breast cancer and total mortality in women with a family history of breast cancer. An 127 (11): 973-80, 1997.Â [PUBMED Abstract]

29. Stanford JL, Weiss NS, Voigt LF, et al.: Combined estrogen and progestin hormone therapy in relation to risk of breast cancer in middle-aged women. JAMA 274 (2): 13 [PUBMED Abstract]

30. Colditz GA, Egan KM, Stampfer MJ: Hormone replacement therapy and risk of brea results from epidemiologic studies. Am J Obstet Gynecol 168 (5): 1473-80, 1993.Â Abstract]

31. Gorsky RD, Koplan JP, Peterson HB, et al.: Relative risks and benefits of long-term replacement therapy: a decision analysis. Obstet Gynecol 83 (2): 161-6, 1994.Â [PU

32. Rebbeck TR, Friebel T, Wagner T, et al.: Effect of short-term hormone replacement breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 anc mutation carriers: the PROSE Study Group. J Clin Oncol 23 (31): 7804-10, 2005.Â Abstract]

33. Helzlsouer KJ, Harris EL, Parshad R, et al.: Familial clustering of breast cancer: pos between DNA repair proficiency and radiation exposure in the development of breas Cancer 64 (1): 14-7, 1995.Â [PUBMED Abstract]

34. Helzlsouer KJ, Harris EL, Parshad R, et al.: DNA repair proficiency: potential susce breast cancer. J Natl Cancer Inst 88 (11): 754-5, 1996.Â [PUBMED Abstract]

35. Abbott DW, Thompson ME, Robinson-Benion C, et al.: BRCA1 expression restores resistance in BRCA1-defective cancer cells through enhancement of transcription-c repair. J Biol Chem 274 (26): 18808-12, 1999.Â [PUBMED Abstract]

36. Abbott DW, Freeman ML, Holt JT: Double-strand break repair deficiency and radiati BRCA2 mutant cancer cells. J Natl Cancer Inst 90 (13): 978-85, 1998.Â [PUBMED Al

37. Easton DF: Cancer risks in A-T heterozygotes. Int J Radiat Biol 66 (6 Suppl): S177- [PUBMED Abstract]

38. Kleihues P, SchÃ¤uble B, zur Hausen A, et al.: Tumors associated with p53 germlin synopsis of 91 families. Am J Pathol 150 (1): 1-13, 1997.Â [PUBMED Abstract]

39. Pierce LJ, Strawderman M, Narod SA, et al.: Effect of radiotherapy after breast-con treatment in women with breast cancer and germline BRCA1/2 mutations. J Clin On 3360-9, 2000.Â [PUBMED Abstract]

40. Narod SA, Lubinski J, Ghadirian P, et al.: Screening mammography and risk of brea BRCA1 and BRCA2 mutation carriers: a case-control study. Lancet Oncol 7 (5): 402 [PUBMED Abstract]

41. Andrieu N, Easton DF, Chang-Claude J, et al.: Effect of chest X-rays on the risk of b among BRCA1/2 mutation carriers in the international BRCA1/2 carrier cohort study the EMBRACE, GENEPSO, GEO-HEBON, and IBCCS Collaborators' Group. J Clin 3361-6, 2006.Â [PUBMED Abstract]

42. Smith-Warner SA, Spiegelman D, Yaun SS, et al.: Alcohol and breast cancer in wor analysis of cohort studies. JAMA 279 (7): 535-40, 1998.Â [PUBMED Abstract]

43. Hamajima N, Hirose K, Tajima K, et al.: Alcohol, tobacco and breast cancer--collabc reanalysis of individual data from 53 epidemiological studies, including 58,515 wom cancer and 95,067 women without the disease. Br J Cancer 87 (11): 1234-45, 2002 Abstract]

44. McGuire V, John EM, Felberg A, et al.: No increased risk of breast cancer associate consumption among carriers of BRCA1 and BRCA2 mutations ages <50 years. Car Biomarkers Prev 15 (8): 1565-7, 2006.Â [PUBMED Abstract]

45. McTiernan A: Behavioral risk factors in breast cancer: can risk be modified? Oncolo 34, 2003.Â [PUBMED Abstract]

46. King MC, Marks JH, Mandell JB, et al.: Breast and ovarian cancer risks due to inher BRCA1 and BRCA2. Science 302 (5645): 643-6, 2003.Â [PUBMED Abstract]

47. Chen J, Pee D, Ayyagari R, et al.: Projecting absolute invasive breast cancer risk in with a model that includes mammographic density. J Natl Cancer Inst 98 (17): 1215 [PUBMED Abstract]

48. Dupont WD, Page DL, Parl FF, et al.: Long-term risk of breast cancer in women witl N Engl J Med 331 (1): 10-5, 1994.Â [PUBMED Abstract]

49. Boyd NF, Byng JW, Jong RA, et al.: Quantitative classification of mammographic de breast cancer risk: results from the Canadian National Breast Screening Study. J Nz 87 (9): 670-5, 1995.Â [PUBMED Abstract]

50. Byrne C, Schairer C, Wolfe J, et al.: Mammographic features and breast cancer risk time, age, and menopause status. J Natl Cancer Inst 87 (21): 1622-9, 1995.Â [PUBI

51. Pankow JS, Vachon CM, Kuni CC, et al.: Genetic analysis of mammographic breast women: evidence of a gene effect. J Natl Cancer Inst 89 (8): 549-56, 1997.Â [PUBM

52. Boyd NF, Lockwood GA, Martin LJ, et al.: Mammographic densities and risk of brea among subjects with a family history of this disease. J Natl Cancer Inst 91 (16): 140 [PUBMED Abstract]

53. Vachon CM, King RA, Atwood LD, et al.: Preliminary sibpair linkage analysis of perc mammographic density. J Natl Cancer Inst 91 (20): 1778-9, 1999.Â [PUBMED Abstrac

54. Ambrosone CB, Freudenheim JL, Graham S, et al.: Cigarette smoking, N-acetyltran genetic polymorphisms, and breast cancer risk. JAMA 276 (18): 1494-501, 1996.Â

55. Brunet JS, Ghadirian P, Rebbeck TR, et al.: Effect of smoking on breast cancer in c BRCA1 or BRCA2 genes. J Natl Cancer Inst 90 (10): 761-6, 1998.Â [PUBMED Abstra

56. Ghadirian P, Lubinski J, Lynch H, et al.: Smoking and the risk of breast cancer amoi BRCA mutations. Int J Cancer 110 (3): 413-6, 2004.Â [PUBMED Abstract]

57. Whittemore AS, Harris R, Itnyre J: Characteristics relating to ovarian cancer risk: co analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in whit Collaborative Ovarian Cancer Group. Am J Epidemiol 136 (10): 1184-203, 1992.Â |

58. John EM, Whittemore AS, Harris R, et al.: Characteristics relating to ovarian cancer collaborative analysis of seven U.S. case-control studies. Epithelial ovarian cancer i Collaborative Ovarian Cancer Group. J Natl Cancer Inst 85 (2): 142-7, 1993.Â [PUB

59. Amos CI, Struewing JP: Genetic epidemiology of epithelial ovarian cancer. Cancer 7 566-72, 1993.Â [PUBMED Abstract]

60. Modan B, Hartge P, Hirsh-Yechezkel G, et al.: Parity, oral contraceptives, and the ri cancer among carriers and noncarriers of a BRCA1 or BRCA2 mutation. N Engl J M 40, 2001.Â [PUBMED Abstract]

61. Brinton LA, Lamb EJ, Moghissi KS, et al.: Ovarian cancer risk after the use of ovulat drugs. Obstet Gynecol 103 (6): 1194-203, 2004.Â [PUBMED Abstract]

62. Rodriguez C, Patel AV, Calle EE, et al.: Estrogen replacement therapy and ovarian in a large prospective study of US women. JAMA 285 (11): 1460-5, 2001.Â [PUBME

63. Riman T, Dickman PW, Nilsson S, et al.: Hormone replacement therapy and the risk epithelial ovarian cancer in Swedish women. J Natl Cancer Inst 94 (7): 497-504, 20(Abstract]

64. Lacey JV Jr, Mink PJ, Lubin JH, et al.: Menopausal hormone replacement therapy a ovarian cancer. JAMA 288 (3): 334-41, 2002.Â [PUBMED Abstract]

65. Anderson GL, Judd HL, Kaunitz AM, et al.: Effects of estrogen plus progestin on gyı cancers and associated diagnostic procedures: the Women's Health Initiative rando JAMA 290 (13): 1739-48, 2003.Â [PUBMED Abstract]

66. Tortolero-Luna G, Mitchell MF: The epidemiology of ovarian cancer. J Cell Biochem 7, 1995.Â [PUBMED Abstract]

67. Hankinson SE, Hunter DJ, Colditz GA, et al.: Tubal ligation, hysterectomy, and risk cancer. A prospective study. JAMA 270 (23): 2813-8, 1993.Â [PUBMED Abstract]

68. Rutter JL, Wacholder S, Chetrit A, et al.: Gynecologic surgeries and risk of ovarian with BRCA1 and BRCA2 Ashkenazi founder mutations: an Israeli population-based study. J Natl Cancer Inst 95 (14): 1072-8, 2003.Â [PUBMED Abstract]

69. Kauff ND, Satagopan JM, Robson ME, et al.: Risk-reducing salpingo-oophorectomy a BRCA1 or BRCA2 mutation. N Engl J Med 346 (21): 1609-15, 2002.Â [PUBMED Al

70. Rebbeck TR, Lynch HT, Neuhausen SL, et al.: Prophylactic oophorectomy in carrie BRCA2 mutations. N Engl J Med 346 (21): 1616-22, 2002.Â [PUBMED Abstract]

71. Narod SA, Risch H, Moslehi R, et al.: Oral contraceptives and the risk of hereditary Hereditary Ovarian Cancer Clinical Study Group. N Engl J Med 339 (7): 424-8, 199 Abstract]

72. Narod SA, Sun P, Ghadirian P, et al.: Tubal ligation and risk of ovarian cancer in ca or BRCA2 mutations: a case-control study. Lancet 357 (9267): 1467-70, 2001.Â [PU

73. Whittemore AS, Balise RR, Pharoah PD, et al.: Oral contraceptive use and ovarian among carriers of BRCA1 or BRCA2 mutations. Br J Cancer 91 (11): 1911-5, 2004.. Abstract]

74. McGuire V, Felberg A, Mills M, et al.: Relation of contraceptive and reproductive his cancer risk in carriers and noncarriers of BRCA1 gene mutations. Am J Epidemiol 1 2004.Â [PUBMED Abstract]

75. Claus EB, Risch N, Thompson WD: Autosomal dominant inheritance of early-onset Implications for risk prediction. Cancer 73 (3): 643-51, 1994.Â [PUBMED Abstract]

76. Claus EB, Risch N, Thompson WD: The calculation of breast cancer risk for women degree family history of ovarian cancer. Breast Cancer Res Treat 28 (2): 115-20, 19 Abstract]

77. Gail MH, Brinton LA, Byar DP, et al.: Projecting individualized probabilities of develc cancer for white females who are being examined annually. J Natl Cancer Inst 81 (2 1989.Â [PUBMED Abstract]

78. Domchek SM, Eisen A, Calzone K, et al.: Application of breast cancer risk predictio clinical practice. J Clin Oncol 21 (4): 593-601, 2003.Â [PUBMED Abstract]

79. Rubinstein WS, O'Neill SM, Peters JA, et al.: Mathematical modeling for breast can assessment. State of the art and role in medicine. Oncology (Huntingt) 16 (8): 1082 1094, 1097-9, 2002.Â [PUBMED Abstract]

80. Rhodes DJ: Identifying and counseling women at increased risk for breast cancer. M 77 (4): 355-60; quiz 360-1, 2002.Â [PUBMED Abstract]

81. Bondy ML, Lustbader ED, Halabi S, et al.: Validation of a breast cancer risk assess women with a positive family history. J Natl Cancer Inst 86 (8): 620-5, 1994.Â [PUB

82. Spiegelman D, Colditz GA, Hunter D, et al.: Validation of the Gail et al. model for pr

individual breast cancer risk. J Natl Cancer Inst 86 (8): 600-7, 1994.Â [PUBMED Abst

83. Rockhill B, Spiegelman D, Byrne C, et al.: Validation of the Gail et al. model of brea prediction and implications for chemoprevention. J Natl Cancer Inst 93 (5): 358-66, [PUBMED Abstract]

84. Costantino JP, Gail MH, Pee D, et al.: Validation studies for models projecting the ri and total breast cancer incidence. J Natl Cancer Inst 91 (18): 1541-8, 1999.Â [PUBM

85. Bondy ML, Newman LA: Breast cancer risk assessment models: applicability to Afri women. Cancer 97 (1 Suppl): 230-5, 2003.Â [PUBMED Abstract]

86. McTiernan A, Kuniyuki A, Yasui Y, et al.: Comparisons of two breast cancer risk est women with a family history of breast cancer. Cancer Epidemiol Biomarkers Prev 1(2001.Â [PUBMED Abstract]

87. Tyrer J, Duffy SW, Cuzick J: A breast cancer prediction model incorporating familial risk factors. Stat Med 23 (7): 1111-30, 2004.Â [PUBMED Abstract]

88. Antoniou AC, Pharoah PP, Smith P, et al.: The BOADICEA model of genetic suscep and ovarian cancer. Br J Cancer 91 (8): 1580-90, 2004.Â [PUBMED Abstract]

89. Barlow WE, White E, Ballard-Barbash R, et al.: Prospective breast cancer risk predi women undergoing screening mammography. J Natl Cancer Inst 98 (17): 1204-14, [PUBMED Abstract]

90. Tice JA, Cummings SR, Ziv E, et al.: Mammographic breast density and the Gail mc cancer risk prediction in a screening population. Breast Cancer Res Treat 94 (2): 11 [PUBMED Abstract]

^ Back to Top

< Previous Section | Next Section >

Genetics of Prostate Cancer (PDQ®)

Last Modified: 12/19/2008

Prostate Cancer Risk Assessment

Risk Assessment and Analysis
Genetic Testing

The purpose of this section is to describe current approaches to assessing and counseling patients about susceptibility to prostate cancer. Genetic counseling for men at increased risk of prostate cancer encompasses all of the elements of genetic counseling for other hereditary cancers. (Refer to the PDQ summary on Cancer Genetics Risk Assessment and Counseling for more information.) The components of genetic counseling include concepts of risk for prostate cancer, reinforcing the importance of detailed family history, pedigree analysis to derive age-related risk, and offering participation in research studies to those individuals who have multiple affected family members.[1,2] Genetic testing for prostate cancer susceptibility is not available outside of the context of a research study. Families with prostate cancer can be referred to ongoing research studies; however, these studies will not provide individual genetic results to participants.

Prostate cancer will affect an estimated 1 in 6 American men over their lifetime. Currently, evidence exists to support the hypothesis that approximately 5% to 10% of all prostate cancer is due to rare autosomal dominant prostate cancer susceptibility genes.[3,4] The proportion of prostate cancer associated with an inherited susceptibility may be even larger.[5-7] Men are generally considered to be candidates for genetic counseling regarding prostate cancer risk if they have a family history of prostate cancer. The Hopkins Criteria provide a working definition of hereditary prostate cancer families.[8] The three criteria include:

1. Three or more first-degree relatives (father, brother, son),
2. Three successive generations of either the maternal or paternal lineages, and/or
3. At least two relatives affected at age 55 years or younger.

Families need to fulfill only one of these criteria to be considered to have hereditary prostate cancer. One study investigated attitudes regarding prostate cancer susceptibility among sons of men with prostate cancer.[9] They found that 90% of sons were interested in knowing if there is an inherited susceptibility to prostate cancer and would be likely to undergo screening as well as consider genetic testing if there was a family history of prostate cancer; however, similar high levels of interest in genetic testing for other hereditary cancer syndromes have not generally been borne out in testing uptake once the clinical genetic test becomes available.

Risk Assessment and Analysis

Assessment of a man concerned about his inherited risk of prostate cancer should include taking a detailed family history, eliciting information regarding personal prostate cancer risk factors, documenting other medical problems, and evaluating genetics-related psychosocial issues.

Family history documentation is based on construction of a pedigree, and generally includes:

- The history of cancer in both maternal and paternal bloodlines.
- All primary cancer diagnoses (not just prostate cancer) and ages at onset.
- Race and ethnicity.
- Other health problems including benign prostatic hypertrophy.[10]

(Refer to the Documenting the family history section in the PDQ summary on Cancer Genetics Risk Assessment and Counseling for a more detailed description of taking a family history.)

Report to Nation Finds Declines in Cancer Incidence, Death Rates
High Dose Chemotherapy Prolongs Survival for Leukemia
Prostate Cancer Study Shows No Benefit for Selenium, Vitamin E
The Nation's Investment in Cancer Research FY 2009
Past Highlights

Analysis of the family history generally consists of four components:

1. Evaluation of the pattern of cancers in the family to identify cancer clusters, which might suggest a known inherited cancer syndrome. In addition to site-specific prostate cancer, other cancer susceptibility syndromes include prostate cancer as a component tumor (e.g., Hereditary Breast/Ovarian Cancer syndrome [associated with mutations in *BRCA1* and *BRCA2*]).

2. Assessment for genetic transmission. The pedigree should be assessed for evidence of both autosomal dominant and X-linked inheritance, which may be associated with a higher likelihood of an inherited susceptibility to prostate cancer. Autosomal dominant transmission is characterized by the presence of affected family members in sequential generations, with approximately 50% of males in each generation affected with prostate cancer. X-linked inheritance is suggested by apparent transmission of susceptibility from affected males in the maternal lineage. Refer to the Analysis of the Family History section in the PDQ summary on Cancer Genetics Risk Assessment and Counseling for more information.

3. Age at onset of prostate cancer in family. An inherited susceptibility to prostate cancer may be likely in families with early-onset (inconsistently defined) prostate cancer.[11] However, genetic research is also underway in families with an older age of prostate cancer onset. In the aggregate, the data are inconsistent relative to whether hereditary prostate cancer is routinely characterized by a younger-than-usual age at diagnosis.

4. Risk assessment based on family and epidemiological studies. Multiple studies have reported that first-degree relatives of men affected with prostate cancer are two to three times more likely to develop prostate cancer than are men in the general population. In some studies, the relative risk of prostate cancer is highest among families who develop prostate cancer at an early age, consistent with other cancer susceptibility syndromes where early age at onset is a common feature. It has been estimated that male relatives of men diagnosed with prostate cancer younger than 53 years have a 40% lifetime cumulative risk of developing prostate cancer.[12] A population-based case-control study of more than 1,500 cases and 1,600 controls, in which Caucasians, African Americans, and Asian Americans were studied, reported an odds ratio of 2.5 for men with an affected first-degree relative after adjusting for age and ethnicity.[13] For men with a brother and father or son affected with prostate cancer, the relative risk was estimated to be 6.4.

A number of studies have examined the accuracy of the family history of prostate cancer provided by men with prostate cancer. This has clinical importance when risk assessments are based on unverified family history information. In an Australian study of 154 unaffected men with a family history of prostate cancer, self-reported family history was verified from cancer registry data in 89.6% of cases.[14] Accuracy of age at diagnosis within a 3-year range was correct in 83% of the cases, and accuracy of age at diagnosis within a 5-year range was correct in 93% of the cases. Self-reported family history from men younger than 55 years and reports about first-degree relatives had the highest degree of accuracy.[14] Self-reported family history of prostate cancer, however, may not be reliably reported over time,[15] which underscores the need to verify objectively reported prostate cancer diagnoses when trying to determine whether a patient has a significant family history.

The personal health and risk-factor history includes, but is not limited to:

- Family history.
- Age.
- Race.
- Current and past diet history, including fat intake.
- Current and past use of drugs that can affect prostatic growth, such as steroids (e.g., finasteride [Proscar]).
- Current and past use of complementary and alternative medications (e.g., saw palmetto, PC-SPES).[16] (For more information on PC-SPES, refer to the PDQ complementary and alternative medicine summary on PC-SPES.)

The most definitive risk factors for prostate cancer are age, race, and family history.[17] The correlation between other risk factors and prostate cancer risk is not clearly established. Despite this limitation, cancer risk counseling is an educational process that provides details regarding the state of the knowledge of prostate cancer risk factors. The discussion regarding these other risk factors should be individualized to incorporate the consultand's personal health and risk factor history. (For a more detailed description of prostate cancer risk factors, refer to the Risk Factors for Prostate Cancer section of this summary.)

The psychosocial assessment in this context might include evaluation of:

- Level of psychological distress.
- Perceived risk of prostate cancer.
- Past history of depression, anxiety, or other mental illness.

One study found that psychological distress was greater among men attending prostate cancer screening who had a family history of the disease, particularly if they also reported an overestimation of prostate cancer risk. Psychological distress and elevated risk perception may influence adherence to cancer screening and risk management strategies. Consultation with a mental health professional may be valuable if serious psychosocial issues are identified.[18]

Genetic Testing

At this time, clinical genetic testing to detect inherited prostate cancer predisposition is not available. None of the candidate susceptibility genes have been unequivocally associated with prostate cancer predisposition. (Refer to the Prostate Cancer Susceptibility Loci section of this summary for more information.) For families suspected of having an inherited susceptibility to prostate cancer, participation in ongoing research studies investigating the genetic basis of inherited prostate cancer susceptibility can be considered.

References

1. Nieder AM, Taneja SS, Zeegers MP, et al.: Genetic counseling for prostate cancer risk. Clin Genet 63 (3): 169-76, 2003. [PUBMED Abstract]

2. Bruner DW, Baffoe-Bonnie A, Miller S, et al.: Prostate cancer risk assessment program. A model for the early detection of prostate cancer. Oncology (Huntingt) 13 (3): 325-34; discussion 337-9, 343-4 pas, 1999. [PUBMED Abstract]

3. Steinberg GD, Carter BS, Beaty TH, et al.: Family history and the risk of prostate cancer. Prostate 17 (4): 337-47, 1990. [PUBMED Abstract]

4. Carter BS, Beaty TH, Steinberg GD, et al.: Mendelian inheritance of familial prostate cancer. Proc Natl Acad Sci U S A 89 (8): 3367-71, 1992. [PUBMED Abstract]

5. Lesko SM, Rosenberg L, Shapiro S: Family history and prostate cancer risk. Am J Epidemiol 144 (11): 1041-7, 1996. [PUBMED Abstract]

6. Grönberg H, Damber L, Damber JE, et al.: Segregation analysis of prostate cancer in Sweden: support for dominant inheritance. Am J Epidemiol 146 (7): 552-7, 1997. [PUBMED Abstract]

7. Schaid DJ, McDonnell SK, Blute ML, et al.: Evidence for autosomal dominant inheritance of prostate cancer. Am J Hum Genet 62 (6): 1425-38, 1998. [PUBMED Abstract]

8. Carter BS, Bova GS, Beaty TH, et al.: Hereditary prostate cancer: epidemiologic and clinical features. J Urol 150 (3): 797-802, 1993. [PUBMED Abstract]

9. Bratt O, Kristoffersson U, Lundgren R, et al.: Sons of men with prostate cancer: their attitudes regarding possible inheritance of prostate cancer, screening, and genetic testing. Urology 50 (3): 360-5, 1997. [PUBMED Abstract]

10. Pienta KJ, Esper PS: Risk factors for prostate cancer. Ann Intern Med 118 (10): 793-803, 1993. [PUBMED Abstract]

11. Giovannucci E: How is individual risk for prostate cancer assessed? Hematol Oncol Clin North Am 10 (3): 537-48, 1996. [PUBMED Abstract]

12. Neuhausen SL, Skolnick MH, Cannon-Albright L: Familial prostate cancer studies in Utah. Br J Urol 79 (Suppl 1): 15-20, 1997. [PUBMED Abstract]

13. Whittemore AS, Wu AH, Kolonel LN, et al.: Family history and prostate cancer risk in black, white, and Asian men in the United States and Canada. Am J Epidemiol 141 (8): 732-40, 1995. [PUBMED Abstract]

14. Gaff CL, Aragona C, MacInnis RJ, et al.: Accuracy and completeness in reporting family history of prostate cancer by unaffected men. Urology 63 (6): 1111-6, 2004. [PUBMED Abstract]

15. Weinrich SP, Faison-Smith L, Hudson-Priest J, et al.: Stability of self-reported family history of prostate cancer among African American men. J Nurs Meas 10 (1): 39-46, 2002 Spring-Summer. [PUBMED Abstract]

16. Barqawi A, Gamito E, O'Donnell C, et al.: Herbal and vitamin supplement use in a prostate cancer screening population. Urology 63 (2): 288-92, 2004. [PUBMED Abstract]

17. Stanford JL, Stephenson RA, Coyle LM, et al., eds.: Prostate Cancer Trends 1973-1995. Bethesda, Md: National Cancer Institute, 1999. NIH Pub. No. 99-4543. Also available online. Last accessed

March 5, 2007.

18. Taylor KL, DiPlacido J, Redd WH, et al.: Demographics, family histories, and psychological characteristics of prostate carcinoma screening participants. Cancer 85 (6): 1305-12, 1999. [PUBMED Abstract]

Back to Top

< Previous Section | Next Section >

Skin Cancer Screening (PDQ®)

Significance

Incidence and Mortality

Skin cancer is the most common cancer in the United States, affecting more than 1,000,00(every year. It accounts for more than 10,000 deaths annually.[1]

Skin cancers are easily detected clinically and are often cured by excisional biopsy alone. T mean that they are unimportant or can be neglected without adverse consequences. When can be disfiguring and/or cause death.

There are three major types of skin cancer: basal cell carcinoma, squamous cell carcinoma melanoma. Basal cell carcinoma has the highest incidence and melanoma has the lowest. I squamous cell carcinomas have an excellent prognosis, but persons diagnosed with these nonmelanomatous skin cancers are at higher risk for developing additional skin cancers.[2] which is the focus of this summary, accounts for approximately three-fourths of all skin can(

Mortality from melanoma increased after the 1970s, especially in white males.[3,4] In the 19 mortality rates stabilized. In 2008, it is estimated that 62,480 individuals are expected to de melanoma, and about 8,420 are expected to die of this disease.[1] In the United States, obs increased 126% between 1973 and 1995, at a rate of approximately 6% per year,[5] though appear also to have stabilized in the 1990s.[4] A study of skin biopsy rates in relation to me incidence rates obtained from the Surveillance, Epidemiology, and End Results Program of Cancer Institute indicated that much of the observed increase in incidence between 1986 a confined to local disease and was most likely caused by overdiagnosis as a result of increa rates during this period.[6]

Risk Factors

The incidence of melanoma rises rapidly in Caucasians after age 20 years. Fair-skinned inc exposed to the sun are at higher risk. The best defense against skin cancer is protection fr ultraviolet light, though the effectiveness of sunscreens in preventing melanoma has been c (Refer to the PDQ summary on Prevention of Skin Cancer for more information.) Individuals types of pigmented lesions (dysplastic or atypical nevi), with several large nondysplastic ne small nevi, or with moderate freckling have a twofold to threefold increased risk of developi Individuals with familial dysplastic nevus syndrome or with several dysplastic or atypical ne (>fivefold) risk of developing melanoma.[8]

References

1. American Cancer Society.: Cancer Facts and Figures 2008. Atlanta, Ga: American (2008. Also available online. Last accessed October 1, 2008.

Death Rates
High Dose Chemotherapy Prolongs Survival for Leukemia
Prostate Cancer Study Shows No Benefit for Selenium, Vitamin E
The Nation's Investment in Cancer Research FY 2009
Past Highlights

2. Karagas MR, Greenberg ER, Mott LA, et al.: Occurrence of other cancers among pa basal cell and squamous cell skin cancer. Cancer Epidemiol Biomarkers Prev 7 (2): [PUBMED Abstract]

3. Wingo PA, Ries LA, Rosenberg HM, et al.: Cancer incidence and mortality, 1973-19 card for the U.S. Cancer 82 (6): 1197-207, 1998. [PUBMED Abstract]

4. Hall HI, Miller DR, Rogers JD, et al.: Update on the incidence and mortality from me United States. J Am Acad Dermatol 40 (1): 35-42, 1999. [PUBMED Abstract]

5. Ries LA, Kosary CL, Hankey BF, et al., eds.: SEER Cancer Statistics Review 1973- Md: National Cancer Institute, 1998.

6. Welch HG, Woloshin S, Schwartz LM: Skin biopsy rates and incidence of melanoma based ecological study. BMJ 331 (7515): 481, 2005. [PUBMED Abstract]

7. Dennis LK, Beane Freeman LE, VanBeek MJ: Sunscreen use and the risk for melar quantitative review. Ann Intern Med 139 (12): 966-78, 2003. [PUBMED Abstract]

8. Gandini S, Sera F, Cattaruzza MS, et al.: Meta-analysis of risk factors for cutaneous Common and atypical naevi. Eur J Cancer 41 (1): 28-44, 2005. [PUBMED Abstract]

^ Back to Top

< Previous Section | Next Section >

Screening

Introduction

The Developmental Therapeutics Program (DTP) operates a progressive, tiered *in vitro* and *in vivo* anti-cancer compound screening program for single pure compounds with the goal of identifying and evaluating novel chemical leads and biological mechanisms of action. The program does not support screening of chemical libraries. The DTP screens include the NCI 60 cell line screen and, as appropriate, the hollow fiber assay and relevant human tumor xenograft and rodent tumor models. Information on the experimental details for the screens, the overall DTP testing paradigm, instructions on submitting compounds and the execution of confidentiality agreements with NCI can be found at the links below. Please note that DTP no longer routinely performs anti-angiogenesis evaluations. In addition, the anti-HIV screen is no longer operational although **Archival Anti-HIV Screening Data** is available. Researchers interested in NIH anti-viral screening resources are referred to the National Institute of Allergy and Infectious Diseases (NIAID) under **NIAID Resources for Researchers**.

Screening Information

In Vitro Testing

- Tumor Cell Line Screen

In Vivo Testing

- Acute Toxicity Determination
- Hollow Fiber Assay
- Tumor Xenograft Models

Anti-Cancer Screening Paradigm

- This printable chart (pdf) summarizes the DTP anti-cancer compound screening services decision tree along with a color-coded key indicating the communication method, between DTP and suppliers, for decisions and data transfer.

Discreet Screening Agreement

- Confidentiality Agreement Forms

Submission of Purified Compounds

- Instructions for submission of purified natural products and synthetic compounds for tumor cell line screening.

Screening Services

Cell Lines In The *In Vitro* Screen

Note: This is a list of the 60 human cancer cell lines used in the screen and maintained at NCI-Frederick. Additional lines evaluated for use in the screen and currently available are listed separately at the bottom of the page.

Please note the links for more information on the SNB-19, U251, NCI/ADR-RES, and MDA-MB-435 cell lines.

- MDA-MB-435
- U251
- SNB-19
- NCI/ADR-RES

Cell Line Name	Panel Name	Doubling Time	Inoculation Density
CCRF-CEM	Leukemia	26.7	40000
HL-60(TB)	Leukemia	28.6	40000
K-562	Leukemia	19.6	5000
MOLT-4	Leukemia	27.9	30000
RPMI-8226	Leukemia	33.5	20000
SR	Leukemia	28.7	20000
A549/ATCC	Non-Small Cell Lung	22.9	7500
EKVX	Non-Small Cell Lung	43.6	20000
HOP-62	Non-Small Cell Lung	39	10000
HOP-92	Non-Small Cell Lung	79.5	20000
NCI-H226	Non-Small Cell Lung	61	20000
NCI-H23	Non-Small Cell Lung	33.4	20000
NCI-H322M	Non-Small Cell Lung	35.3	20000
NCI-H460	Non-Small Cell Lung	17.8	7500
NCI-H522	Non-Small Cell Lung	38.2	20000
COLO 205	Colon	23.8	15000
HCC-2998	Colon	31.5	15000
HCT-116	Colon	17.4	5000
HCT-15	Colon	20.6	10000
HT29	Colon	19.5	5000
KM12	Colon	23.7	15000
SW-620	Colon	20.4	10000
SF-268	CNS	33.1	15000
SF-295	CNS	29.5	10000
SF-539	CNS	35.4	15000
SNB-19	CNS (For more Information)	34.6	15000

SNB-75	CNS	62.8	20000
U251	CNS (For more information)	23.8	7500
LOX IMVI	Melanoma	20.5	7500
MALME-3M	Melanoma	46.2	20000
M14	Melanoma	26.3	15000
MDA-MB-435	Melanoma (For more information)	25.8	15000
SK-MEL-2	Melanoma	45.5	20000
SK-MEL-28	Melanoma	35.1	10000
SK-MEL-5	Melanoma	25.2	10000
UACC-257	Melanoma	38.5	20000
UACC-62	Melanoma	31.3	10000
IGR-OV1	Ovarian	31	10000
OVCAR-3	Ovarian	34.7	10000
OVCAR-4	Ovarian	41.4	15000
OVCAR-5	Ovarian	48.8	20000
OVCAR-8	Ovarian	26.1	10000
NCI/ADR-RES	Ovarian (For more information)	34	15000
SK-OV-3	Ovarian	48.7	20000
786-0	Renal	22.4	10000
A498	Renal	66.8	25000
ACHN	Renal	27.5	10000
CAKI-1	Renal	39	10000
RXF 393	Renal	62.9	15000
SN12C	Renal	29.5	15000
TK-10	Renal	51.3	15000
UO-31	Renal	41.7	15000
PC-3	Prostate	27.1	7500
DU-145	Prostate	32.3	10000
MCF7	Breast	25.4	10000
MDA-MB-231/ATCC	Breast	41.9	20000
HS 578T	Breast	53.8	20000
MDA-N **Not Available**	Breast	22.5	15000
BT-549	Breast	53.9	20000
T-47D	Breast	45.5	20000

Additional Lines

Cell Line Name	Panel Name	Doubling Time	Inoculation Density
LXFL 529	Non-Small Cell Lung		10000

DMS 114	Small Cell Lung		20000
SHP-77	Small Cell Lung		40000
DLD-1	Colon		50000
KM20L2	Colon		10000
SNB-78	CNS		20000
XF 498	CNS		20000
RPMI-7951	Melanoma		20000
M19-MEL	Melanoma		10000
RXF-631	Renal		10000
SN12K1	Renal		10000
MDA-MB-468	Breast		20000
P388	Leukemia		50000
P388/ADR	Leukemia		50000